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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED: 3/3/10

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/234,182	Hsei et al.
Examiner	**Group Art Unit**
Marianne DiBrino	1644

X Responsive to communication(s) filed on *Apr 18, 2000*

This action is **FINAL.**

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

X Claim(s) *1-35* is/are pending in the applicat

Of the above, claim(s) *2-4, 6, 7, 9, 11-14, 16, 17, 20, 22, 23, and 27* is/are withdrawn from consideration

Claim(s) _____ is/are allowed.

X Claim(s) *1, 5, 8, 10, 15, 18, 19, 21, 24-26, and 28-35* is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received _____

X Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s) _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's amendment filed 4/18/00 is acknowledged and has been entered.

Claims 1-35 are pending.

2. Restriction to one of the following species is required under 35 U.S.C. § 121:

Applicant is required to elect a specific conjugate consisting of one or more specific antibody fragments (for example, Fab') attached to no more than a specific number of a specific polymer molecules (for instance, no more than 10 non-proteinacious molecules) which has a specific apparent size (for example, at least about 500KD and at least about 8 fold greater than the apparent size of at least one antibody fragment).

These conjugates are distinct because their structures, sizes and physico-chemical properties are different.

3. In addition, Applicant is required to elect a specific species of PEG molecule (for example, single chain PEG) of a specific average molecular weight (for example, average molecular weight of at least about 20kD).

These species are distinct because their size, structures and physico-chemical properties are different.

4. Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

5. Applicant is advised that a response to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. § 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. M.P.E.P. § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

6. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

8. During a telephone conversation with Mr. Richard Love on 5/8/00, a provisional election was made without traverse to prosecute the conjugate exemplified in item #2 above and the PEG exemplified item #3 above. Affirmation of this election must be made by applicant in responding to this Office action.

9. Claims 2-4, 6, 7, 9, 11-14, 16, 17, 20, 22, 23 and 27 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as drawn to non-elected species.

Claims 1, 5, 8, 10, 15, 18, 19, 21, 24-26 and 28-35 are presently being acted upon.

10. The information disclosure statements filed 12/22/99, 10/26/99 and 6/08/99 fail to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the reference cited therein have not been provided by applicant. The information disclosure statements have been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing elements will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

11. The drawings are considered to be informal because they fail to comply with 37 CFR 1.84(a)(1) which requires black and white drawings using India ink or its equivalent.

Photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) or (b)(1) is granted permitting their use as formal drawings. In

the event applicant wishes to use the drawings currently on file as formal drawings, a petition must be filed for acceptance of the photographs or color drawings as formal drawings. Any such petition must be accompanied by the appropriate fee as set forth in 37 CFR 1.17(I), three sets of drawings or photographs, as appropriate, and, if filed under the provisions of 37 CFR 1.84(a)(2), an amendment to the first paragraph of the brief description of the drawings section of the specification which states:

> The file of this patent contains at least one drawing executed in color. Copies of this patent with color drawing(s) will be provided by the Patent and Trademark Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

12. The disclosure is objected to because of the following informality: There are no Y-axis labels on Figs 34C and D or Figs 39, 40, 50A-B, 55A-C and 58A-B. Appropriate correction is required.

13. For the purpose of prior art rejections, the filing date of the instant claim 29 is deemed to be the filing date of the instant application, i.e., 1/20/99 as the parent applications do not support the claimed limitations of the instant application. The protein with the sequence of SEQ ID NO: 62 does not appear to be disclosed in the 60/074,330 and 60/075,467 parent applications.

14. Claims 1, 5, 10, 18, 19, 21 and 30-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the broadly claimed conjugate.

The instant claims encompass a conjugate consisting of an antibody fragment that does not bind antigen covalently coupled to any polymer. There is insufficient disclosure in the specification for such a conjugate.

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1, 5, 10, 18, 19, 21 and 30-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a conjugate consisting of one or more antibody fragments wherein the conjugate binds antigen and wherein the antibody fragments are covalently attached to one or more PEG molecules, does not reasonably provide enablement for a conjugate consisting of one or more antibody fragments covalently coupled to any polymer wherein the conjugate does not bind antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ46 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a conjugate consisting of an antibody fragment wherein the conjugate does not bind antigen and wherein the antibody fragments are covalently attached to any polymer molecule at any position in the antibody. The claims broadly encompass a conjugate comprising an antibody fragment as small as a single amino acid residue of an antibody which would not bind antigen. The claims also encompass a conjugate that would not bind antigen. The claims also encompass any polymer which includes proteins, DNA, plastics, liposomes and so forth (see page 75 of the instant specification), covalently coupled to an antibody.

The specification teaches covalent coupling of PEG to an antibody and Fab', Fab-SH and F(ab')2 of the antibody, wherein the resulting conjugate binds the antigen IL-8 (see pages 216-226). The specification teaches covalent coupling of the polymer to an antibody through the N-terminal amino group and epsilon amino groups found on lysine residues, as well as other amino, imino, carboxyl, sulfhydryl or other hydrophilic groups, or by chemically modifying the lysine with Traut's reagent (see pages 75 and 76). The specification discloses covalent binding to amino groups is accomplished by the known chemistries on page 76 of the specification. The specification fails to enable the covalent coupling of any polymer other than PEG to the antibody or antibody fragments wherein the resulting conjugate binds any antigen or specifically binds IL-8. The specification does not

enable a conjugate consisting of an antibody fragment which binds antigen wherein the antibody is covalently coupled to any polymer besides PEG through the naturally occurring cysteine residue in the light chain or heavy chain or an engineered cysteine residue in regions of the antibody outside the CDRs.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in the proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light chain variable regions, particularly in the CDRs, may dramatically affect antigen binding function as evidenced by Rudikoff et al (PNAS USA 1982, Vol. 79, p 1979). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine binding myeloma protein resulted in the loss of antigen binding function. It is unlikely that antibody fragments as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an antibody have the required binding function. The specification provide insufficient guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Panka et al (PNAS USA 85, 3080, 1988) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity. In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al, Science Vol. 233, pp 747-753, 1986). In addition, the specification does not enable that a conjugate consisting of a functional antibody can be obtained by coupling the polymer to a cysteine residue in the light chain or heavy chain which in the parent antibody formed a disulfide bond.

In addition, a fragment of the heavy chain can be any one of the constant regions and may also be the hinge region. However, the claim language also reads on small amino acid sequences which are incomplete regions of the constant region of the antibody. There is no support in the specification for any or all of the myriad

"fragments" which are encompassed within this language. One of skill in the art would neither expect nor predict the appropriate functioning of the conjugate consisting of an antibody as broadly as it is claimed. Therefore, in view of the lack of guidance in the specification and in view of the unpredictability in the art as evidenced by Rudikoff et al, Panka et al and Amit et al, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 1, 5, 8, 10, 15, 18, 19, 21, 24-26 and 28-35 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1, 8, 10, 15, 18, 19, 21, 24-26 and 28-35 are indefinite in the recitation of "consisting essentially of" because it is not clear what other elements are encompassed that would not effect the basic and novel characteristics of the claimed invention. This term is considered indefinite when used in a compound claim.

b. Claims 1, 8, 10, 15, 18, 19, 21, 24-26 and 28-35 are indefinite in the recitation of "apparent size" because it is not clear what deviations from a molecular weight of "at least about 500 kD" are encompassed by the instant claims.

The amendments must be supported by the specification so as not to add any new matter.

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application

20. Claims 1, 5, 8, 10, 15, 18, 19, 21, 24-26 and 28-35 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 8, 10, 15, 18, 19, 23, 26, 27, 29 and 30 of copending Application No. 09/012,116. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are encompassed by the conjugate of the copending application. Claim 1 in the instant application consists of an antibody fragment(s) covalently attached to a nonproteinaceous polymer, whereas Claim 1 of the '116 Application is drawn to a conjugate consisting of an antibody fragment(s) covalently attached to a polymer. The instant claims 26, 28, 29 and 33-35 are included because: it would have been obvious to use the CDRs from a particular light chain in a humanized antibody conjugate, including in the instant application, the light chain comprising SEQ ID NO: 56 or SEQ ID NO: 62 or a fragment of either one, and it would have been obvious to incorporate a label into the conjugate and to purify the conjugate. Therefore, the two sets of claims would have been prima facie obvious in view of each other to one of ordinary skill in the art at the time the invention was made. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.
>
> (f) he did not himself invent the subject matter sought to be patented.

22. Claims 1, 5, 10, 18, 19, 30, 31 and 32 are rejected under 35 U.S.C. 102(e) as being anticipated by Faanes et al (U.S. Patent No. 5,695,760).

U.S. Patent No. 5,695,760 discloses a conjugate comprising an antibody covalently conjugated to no more than ten PEG molecules which can be up to 40KD each (column 12, lines 62-63, column 22, lines 56-58, Table 1) wherein the apparent size of the conjugate is at least 500 kD (column 19, lines 37-41) and the conjugate comprises a carrier that is sterile (column 19, lines 37-41).

The reference teachings anticipate the claimed invention.

23. Claims 1, 5, 8, 10, 15, 18, 19, 21, 24-26 and 28-35 are rejected under 35 U.S.C. 102(e) as being anticipated by Application Serial No. 09/012,116.

Application Serial No. 09/012,116 discloses the conjugates of the instant claims, including the

limitations of non-proteinaceous polymer, and SEQ ID NOS: 56 and 62 of the instant application.

The reference teachings anticipate the claimed invention.

24. Claims 1, 5, 8, 10, 15, 18, 19, 21, 24-26 and 28-35 are rejected under 35 U.S.C. 102(f) as being anticipated by Application Serial No. 09/012,116.

Application Serial No. 09/012,116 discloses the conjugates of the instant claims, including the limitations of non-proteinaceous polymer, and SEQ ID NOS: 56 and 62 of the instant application.

The reference teachings anticipate the claimed invention.

25. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

26. Claims 1, 5, 8, 10, 15, 18, 19, 21, 26, 28, 29 and 30-35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Braxton (U.S. Patent No. 5,766,897) in view of Doerschuk et al (U.S. Patent No. 5,702,946), Delgado et al (Brit. J. Cancer, Vol. 73, pages 175-182, 1996) and Griffiths et al (U.S. Patent No. 5,670,132).

Braxton teaches conjugates of immunoglobulin covalently attached to the nonproteinaceous polymer PEG (especially column 12, Table 1A), that the PEG moiety attached to the protein may range in molecular weight from about 0.2 kD to 20 kD (especially column 12, lines 50-51), and further that the ratio of PEG to protein is 1:1, 2:1, 5:1, up to 10:1 or 40:1(especially

column 13, lines 4-7). Braxton also teaches that the number of PEG molecules covalently bound per chemically modified protein of the invention may vary widely depending upon the desired protein stability (e.g. serum half-life) and the protein used for chemical modification (especially column 12, lines 55-59) and that the conjugates contain up to a maximum number of PEG moieties bound to the protein without abolishing activity (especially column 12, lines 66-67 and column 13, lines 1-2). Given the teachings of molecular weight and PEGylation ratio discussed supra, Braxton thus teaches a conjugate "wherein the apparent size of the conjugate is at least about 500 kD".

Braxton does not teach that the immunoglobulin of the conjugate is an antibody fragment, a Fab' fragment, nor an antibody fragment comprising an antigen binding site that binds to human IL-8, nor mAb 6G4.2.5, nor humanized antibodies or fragments. Braxton does not teach antibody fragment-PEG conjugates that are radiolabeled or are present within a composition comprising a sterile carrier.

Doerschuk et al disclose anti-IL-8 monoclonal antibodies and Fab' fragments of these antibodies (especially column 1, lines 63-67) as well as humanized antibodies and humanized Fab' fragments (especially column 6, lines 49-61). They also teach the use of these monoclonal antibody fragments for treatment of inflammatory disorders. Doerschuk et al further disclose humanized light chain CDRs derived from the same anti-IL-8 parent antibody used to derive the CDR recited in claim 29 of the instant application (see claims 1,2 and 9 of Doerschuk et al).

Delgado et al disclose that covalent modification of proteins with PEG was the method of choice to overcome the major problems associated with protein therapeutics. They teach increased plasma half-life, increased resistance to proteolysis and substantial reduction in antigenicity/immunogenicity have been found in almost all recombinant and native proteins after PEGylation. Delgado et al also disclose that benefits of PEG modification extend beyond these advantages, such as PEGylated antibodies possessing tumor-localizing properties.

Griffiths et al teach that antibody fragments such as Fab' fragments have faster targeting kinetics than intact immunoglobulin and have a lower occurrence of human immune responses compared to intact IgG molecules (especially column 1, lines 15-19). They also teach conjugates that are to be administered internally to a patient (other than oral administration) are stored under sterile conditions and administered in sterile pharmaceutically acceptable carriers (especially column 5, lines 45-61). They further teach a radiolabeled Fab'-PEG conjugate and it's use in in vivo diagnostics (see column 1, last paragraph and column 2, last paragraph and continuing onto column 3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the

invention was made to have created the claimed invention by substituting the anti-IL-8 Fab' fragments of Doerschuk et al for the immunoglobulin in the conjugate of Braxton. One of ordinary skill in the art would have been motivated to do this because of the disclosure of Doerschuk et al of the usefulness of anti-IL-8 monoclonal antibodies in the treatment of inflammatory disorders, especially in light of the teachings of Delgado et al that covalent modification of proteins with PEG was the method of choice to overcome the major problems associated with protein therapeutics and the advantages of using said conjugates in terms of increased plasma half-life, increased resistance to proteolysis, substantial reduction in antigenicity/immunogenicity, and in light of the teaching of Griffiths that antibody fragments such as Fab' fragments have faster targeting kinetics than intact immunoglobulin and have a lower occurrence of human immune responses compared to intact IgG molecules. One of ordinary skill in the art at the time the invention was made would have been motivated to produce a composition comprising the Fab'-PEG conjugate, such as the one discussed supra, in a sterile pharmaceutically acceptable carrier given the teaching of Griffiths et al of such conjugates administered to patients. One of ordinary skill in the art at the time the invention was made would have been motivated to label a Fab'-PEG conjugate, such as the one discussed supra, with a radiolabel as taught by Griffiths et al, especially in light of their teaching of use for in vivo diagnostics. One of ordinary skill in the art at the time the invention was made would have been motivated to use art-known forms of PEG, such as PEG that is a single chain molecule.

27. Claims 1, 5, 8, 10, 15, 18, 19, 26, 28, 29 and 30-35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Braxton (U.S. Patent No. 5,766,897) in view of Doerschuk et al (U.S. Patent No. 5,702,946)

U.S. Patent No. 5,695,760 discloses a conjugate comprising an antibody or fragment covalently conjugated to no more than ten PEG molecules which can be up to 40KD each (column 12, lines 62-63, column 22, lines 56-58, Table 1) wherein the apparent size of the conjugate is at least 500 kD (column 19, lines 37-41) and the conjugate comprises a carrier that is sterile (column 19, lines 37-41). The '760 patent also discloses that PEG modification of antibody/antibody fragments has benefits such as extending the half-life of the molecule in circulation and to reduce or eliminate the inherent immunogenicity of foreign source proteins used as human therapeutics (especially column 13, lines 25-27 and 50-54).

The '760 patent does not disclose that the immunoglobulin of the conjugate is a Fab' fragment, nor an antibody fragment comprising an antigen binding site that binds to human IL-8, nor mAb 6G4.2.5, nor humanized antibodies or fragments.

Doerschuk et al disclose anti-IL-8 monoclonal antibodies and Fab' fragments of these antibodies (especially column 1, lines 63-67) as well as humanized antibodies and humanized

Fab' fragments (especially column 6, lines 49-61). Doerschuk further discloses the use of these monoclonal antibody fragments for treatment of inflammatory disorders. Doerschuk et al also discloses humanized light chain CDRs derived from the same anti-IL-8 parent antibody used to derive the CDR recited in claim 29 of the instant application (see claims 1,2 and 9 of Doerschuk et al).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention by substituting the anti-IL-8 Fab' fragments of Doerschuk et al for the immunoglobulin in the conjugate of the '760 patent. One of ordinary skill in the art would have been motivated to do this because of disclosure of Doerschuk et al of the usefulness of anti-IL-8 monoclonal antibodies in treatment of inflammatory disorders and because the '760 patent discloses that covalent modification of proteins with PEG was a way to overcome major problems associated with protein therapeutics such as increased plasma half-life and reduction in immunogenicity.

28. Claims 21, 24, 25, are rejected under 35 U.S.C. 103(a) as being unpatentable over as applied to claims 1, 5, 8, 10, 15, 18, 19, 26, 28, 29 and 30-32 above, and further in view of Griffiths et al (U.S. Patent No. 5,670,132).

The '760 patent does not teach antibody fragment-PEG conjugates that are radiolabeled or wherein the covalent structure is free of any matter other than the antibody fragment and the nonproteinaceous polymer molecules that form the conjugate, or wherein PEG is a single chain molecule.

Griffiths et al disclose a radiolabeled Fab'-PEG conjugate and it's use in in vivo diagnostics (see column 1, last paragraph and column 2, last paragraph and continuing onto column 3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to label a Fab'-PEG conjugate, such as the one discussed supra, with a radiolabel as taught by Griffiths et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in light of Griffiths disclosure in vivo diagnostic use. One of ordinary skill in the art at the time the invention was made would have been motivated to use art-known forms of PEG, such as PEG that is a single chain molecule. One of ordinary skill in the art at the time the invention was made would have been motivated to produce a conjugate, wherein the covalent structure of said conjugate was free of any matter other than the antibody fragment, the nonproteinaceous polymer and label molecule to insure purity and potency of the conjugate for therapeutic use.

29. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any

errors of which applicant may become aware of in the specification.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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May 16, 2000

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